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Nanomechanical IR spectroscopy for fast analysis of liquid-dispersed engineered nanomaterials



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ABSTRACT

The proliferated use of engineered nanomaterials (ENMs), e.g. in nanomedicine, calls for novel techniques allowing for fast and sensitive analysis of minute samples. Here we present nanomechanical IR spectroscopy (NAM-IR) for chemical analysis of picograms of ENMs. ENMs are nebulized directly from dispersion and efficiently collected on nanomechanical string resonators through a non-diffusion limited sampling method. Even very small amounts of sample can convert absorbed IR light into a measurable frequency detuning of the string through photothermal heating. An IR absorption spectrum is thus readily obtained by recording this detuning of the resonator over a range of IR wavelengths. Results recorded using NAM-IR agree well with corresponding results obtained through ATR-FTIR, and remarkably, measurement including sample preparation takes only a few minutes, compared to ~2 days sample preparation for ATR-FTIR. Resonator dimensions play an important role in NAM-IR, a relationship which will be elaborated here.

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1. Introduction

Nanomaterials are increasingly designed and engineered for specific purposes, especially in nanomedicine, where engineered nanomaterials (ENMs) form the basis of a wide range of novel drug delivery and other therapeutic systems, as well as entities for precision diagnosis [1,2]. Typically, newly designed ENMs are initially synthesized in research labs in relatively small amounts, and go through multiple rounds of adjustment. Therefore, novel tools for fast chemical analysis of minute samples are at high demand.

Infrared (IR) spectroscopy provides information about molecular structures in a sample, by measuring the fraction of incident IR radiation absorbed by a sample at a particular wavelength. Most compounds exhibit peaks in their mid-IR spectrum between 400 and 4000 cm^{-1} . This characteristic set of peaks, with specific positions and relative intensities, is known as the 'chemical fingerprint' of the compound. IR spectroscopy has been a valuable research tool for decades in various fields, such as pharmacy, forensic science and industrial process control [3–6]. However, conventional

IR spectroscopy techniques such as attenuated total reflectance-Fourier transform IR (ATR-FTIR) spectroscopy still require relatively large sample amounts and extensive sample preparation. A sample mass of 1–6 mg is typically used for ATR-FTIR [7–9], although samples down to 0.25 mg have been analyzed by this method [10]. Aqueous dispersions of e.g. drugs or colloidal systems are typically dried before measurement, since water is known to disturb IR spectroscopic measurements. Depending on sample concentration, freeze-drying enough material for one measurement can take several days.

In this paper, nanomechanical IR spectroscopy (NAM-IR) is demonstrated to be highly suitable for analysis of ENMs, yielding results similar to those obtained with ATR-FTIR, but in a few minutes, sample preparation included. Samples are collected on nanomechanical string resonators and exposed to monochromatic IR light from a quantum cascade laser (QCL). IR light absorbed by the sample is transferred into a measurable frequency detuning of the string, due to photothermal heating. The resonance frequency shift is directly proportional to the absorbed energy. A NAM-IR spectrum is thus readily obtained by recording this photothermal frequency detuning of the resonator.

NAM-IR has the particular benefit of ultra-fast sample preparation, owing to the non-diffusion limited sampling method used to collect material on the strings. Measurement including sample preparation takes only a few minutes, a significant reduction from

Abbreviations: ENMs, engineered nanomaterials; NAM-IR, nanomechanical IR spectroscopy.

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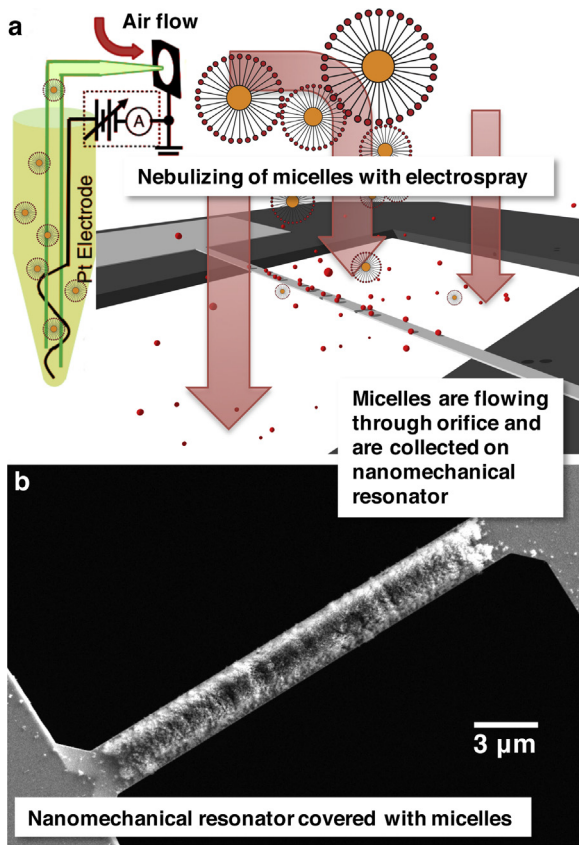


Fig. 1. (a) Schematic drawing of the non-diffusion limited sampling method. The engineered nanoparticles (polymeric micelles in this case) are directly sampled from the liquid dispersion onto the nanomechanical string. An aerosol of the sample is produced by an electro spray. This aerosol is pumped through the orifice in the sensor chip, over which the resonator is spanned. In this way, the nanomechanical resonator functions as a single filter-fiber (Fig. 1) [11,12].

that required for conventional methods. Sampling on strings is done by nebulizing ENMs directly from dispersion using an electro spray or jet nebulizer setup. The aerosol containing the material to be analyzed flows through an orifice in the sensor chip, over which the resonator is spanned. In this way, the nanomechanical resonator functions as a single filter-fiber (Fig. 1) [11,12].

The main mechanisms by which nebulized materials are captured on the resonators are diffusion and inertial impaction (Fig. 2a and b). When a particle is deposited due to diffusion, it is the Brownian motion of the particle that causes it to wiggle out of its trajectory and impact on the fiber, when passing on an adjacent streamline. If a particle has a large enough momentum, it can get deposited by inertial impaction. In this type of deposition, the large particle velocity and/or mass causes it to leave the streamline that bends abruptly around the string and hit the fiber. Inertial impaction can be efficiently exploited for sampling of ENMs on strings, by using high velocities. The small orifice in the sensor chip, featured by the NAM-IR sampling setup, can accelerate the ENM aerosol to velocities in the inertial impaction sampling regime.

The collection efficiency of a single filter-fiber is defined as the fraction of particles collected to the total number of particles that would have passed through the fiber if they had moved on straight lines. The total collection efficiency E_c can be defined as the sum of the collection efficiencies due to diffusion (E_d) and inertial impaction (E_i) [11]:

$$E_c = E_d + E_i = a_1(d_f u)^{-2/3} + a_2 u/d_f, \quad (1)$$

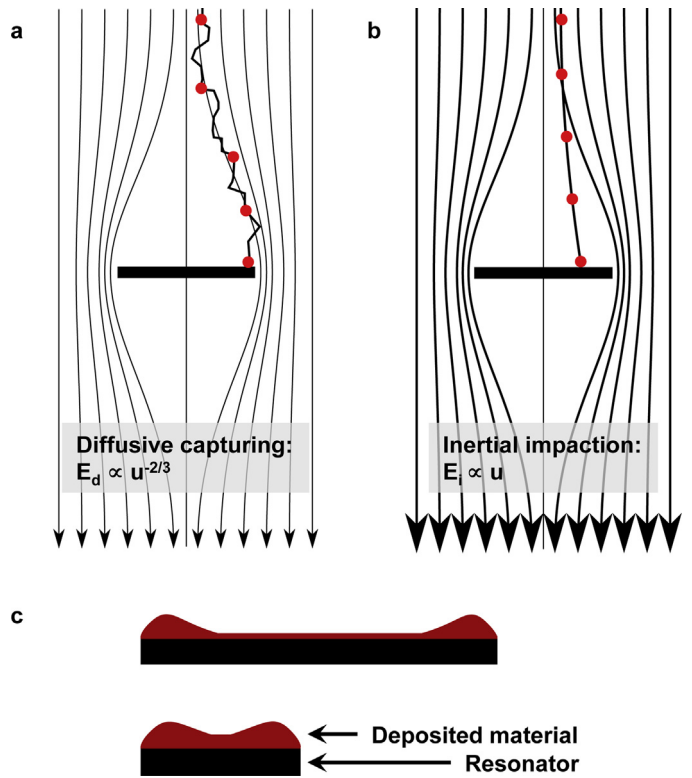


Fig. 2. Particle collection on strings. (a) Diffusive capturing (with collection efficiency E_d) occurs when thermal wiggling of a particle causes it to leave the streamline around the string and deposit on the fiber. (b) Inertial impaction (with collection efficiency E_i) happens, when a particle has a large enough momentum to continue its travel towards the string instead of following the streamlines that bend around the string. If the particle velocity u is sufficiently increased (as indicated by the thick flow lines), the dominant collection mechanism becomes inertial impaction. (c) Particles leaving the streamlines due to either collection mechanism are most likely to hit the string near the edges. Collection on narrow strings is more efficient because of this 'edge effect'.

where d_f is the fiber diameter and u the aerosol velocity. a_1 and a_2 are constants depending on the particle and the fluid in which it is suspended.

At high velocities, collection can be assumed to take place by inertial impaction alone, and Brownian diffusion is thus ignored. In this case, the collection efficiency is

$$E_c = a_2 \frac{u}{d_f}, \quad (2)$$

The collection efficiency is thus directly proportional to particle velocity. Eq. (2) also shows that the collection efficiency increases for narrow fibers. This makes sense, as particles leaving the streamlines are more likely to hit the string near the edges (Fig. 2c).

In order to further appreciate the importance of particle velocity on collection efficiency, we can write the number of particles collected per time as

$$N_t = d_f L C_p E_c u = L C_p a_2 u^2, \quad (3)$$

with the particle number concentration C_p and the fiber length L [11].

The non-diffusion limited sampling method has an up to 100% collection efficiency of the particles flowing in the projection of the string resonator, which means that only very small volumes of dilute sample solutions are necessary to coat the resonator.

Eqs. (1)–(3) demonstrate the importance of geometrical aspects when materials are deposited onto mechanical string resonators by non-diffusion limited sampling. The geometry of the resonators is equally important for their sensitivity, when measuring

photothermal frequency detunings. The relative resonance frequency change of a mechanical string resonator with cross sectional area A and length L , which is exposed to a certain laser power P in its center, can be written as [13]

$$\frac{\Delta f}{f} = -\frac{\alpha E}{\sigma_0 \kappa} \frac{L}{16A} P, \quad (4)$$

with thermal expansion coefficient α , Young's modulus E , tensile pre-stress σ_0 , and thermal conductivity κ , of the string material. With A being the product of string width and string thickness, the relative frequency change becomes directly proportional to fiber length, and inversely proportional to string width. In other words; the resonator is expected to be more sensitive for long and narrow fibers, the same geometrical prerequisites as for efficient sampling.

In this study, sampling experiments demonstrate the importance of resonator dimensions and aerosol velocity, and show that efficient material deposition can be achieved in a few minutes using inertial impaction sampling. The relationship between resonator geometry and sensitivity is illustrated by measurements of resonance frequency shifts of strings of varying widths and lengths subjected to a fixed laser power change. Finally, two examples of how NAM-IR can be employed for chemical analysis of ENMs are given.

2. Material and methods

2.1. Fabrication of nanomechanical resonators

The mechanical string resonators were fabricated by standard cleanroom processing, as previously described [14,11].

2.2. Synthesis of polymeric micelles

Micelles were synthesized by self-assembly of an amphiphilic triblock copolymer, poly(ethylene glycol)-*b*-poly(2-amino ethyl methacrylate)-*b*-poly(coumarin methacrylate) (PEG-*b*-PAEMA-*b*-PCMA) in water. PEG-*b*-PAEMA-*b*-PCMA was synthesized by isolated macroinitiator atom transfer radical polymerization. Self-assembly of the triblock copolymers gave micelles with an average diameter of 45 nm.

2.3. Polyvinylpyrrolidone and polystyrene

Polyvinylpyrrolidone (PVP, 10,000 g/mol) and polystyrene (PS) latex beads (100 nm, 10% w/w in aqueous suspension) were

purchased from Sigma–Aldrich and used without further purification. PVP solutions were prepared with milli-Q water.

2.4. Sampling setup

Aerosols of PEG-*b*-PAEMA-*b*-PCMA micelles were generated either by using an electrospray aerosol generator (Model 3480, TSI), receiving CO₂ (0.1 L/min), and compressed air (1 L/min) through a filtered air supply (Model 3074, TSI), or a basic jet nebulizer, receiving compressed air through a filtered air supply (Model 3074, TSI). The nominal liquid flow rate through the electrospray capillary for aqueous solutions is approximately 66 nL/min. Aerosols of polymers and beads were generated from bulk volumes with the jet nebulizer. In both the electrospray and jet nebulizer setups, the aerosol was led through a sampling chamber containing a sensor chip (Fig. 3 (1)). The strings were spanned over small orifices in the chips.

2.5. Frequency measurements and IR spectroscopy

The sensor chip was mounted in an aluminium vacuum chamber providing electrical connection, a glass window for optical read-out and a zinc selenide window for IR irradiation (Fig. 3 (2)). The resonators were actuated with an external piezoelectric element and read out with a laser-Doppler vibrometer (MSA-500, Polytec GmbH) mounted with a 632.8 nm helium neon readout laser. The nanomechanical resonance frequency was monitored by means of a phase-locked loop (HF2LI-PLL, Zurich Instruments). For NAM-IR measurements, monochromatic IR light was produced by a tunable quantum cascade laser (QCL). The IR reference spectrum was recorded with an ATR-FTIR spectrometer (Spectrum 100, Perkin-Elmer).

3. Results and discussion

3.1. Sampling experiments

Poly(ethylene glycol)-*b*-poly(2-amino ethyl methacrylate)-*b*-poly(coumarin methacrylate) (PEG-*b*-PAEMA-*b*-PCMA) micelles were sampled onto silicon nitride (SiN) string resonators by electrospraying for 5 min, using different flow rates. The initial micelle sample in solution had a concentration of 1 mg/ml. Fig. 4 shows three strings, all 5 μm wide, 50 μm long and 100 nm thick, sampled using velocities of 50, 100, and 185 m/s, respectively. The figure

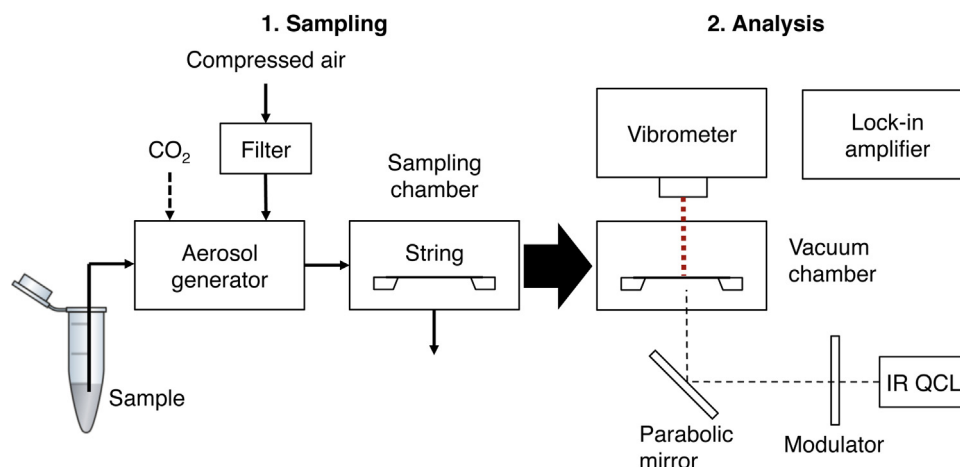


Fig. 3. Schematic overview of the entire NAM-IR setup. 1. Sampling setup. Different aerosol generators were used for different experiments; the electrospray aerosol generator was supplied with both CO₂ and filtered air, while the basic jet nebulizer used only filtered air. 2. Experimental setup used for photothermal recordings of NAM-IR spectra. IR light is focused onto the string using a parabolic mirror, and frequency measurements are carried out using a vibrometer and lock-in amplifier.

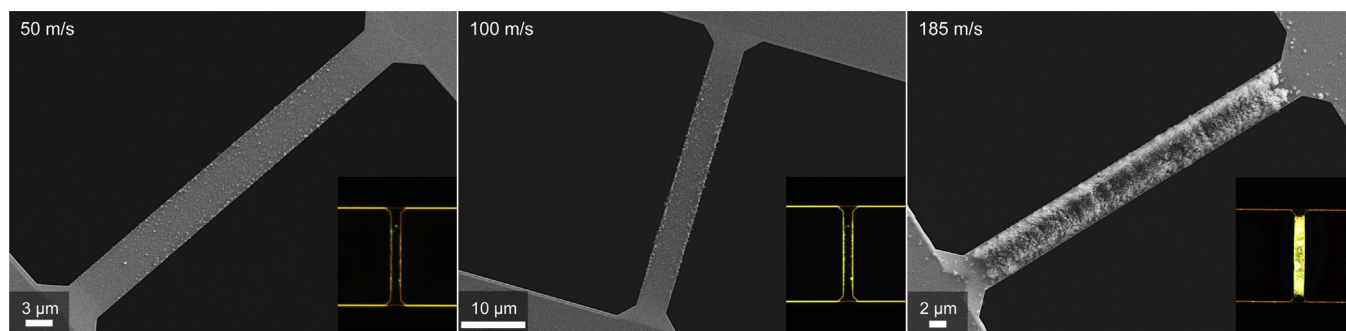


Fig. 4. SEM images and corresponding conventional dark field images of three SiN strings (5 μm wide and 50 μm long) coated with PEG-*b*-PAEMA-*b*-PCMA micelles using increasing aerosol velocities. The aerosol was generated by electrospraying a 1 mg/ml micelle solution.

correlates well with Eq. (3), which predicts the number of particles collected on a resonant filter-fiber per time to increase quadratically with the aerosol velocity. When increasing the velocity from 50 to 100 m/s, the increase in number of collected particles is negligible, except for a small edge effect. However, upon increasing the velocity from 100 to 185 m/s, the increase in deposited material is quite heavy. Fig. 5 shows two narrower strings, 1000 nm wide, but with the same length and thickness as the strings shown in Fig. 4, sampled at 50 and 100 m/s, respectively. Sampling is seen to be more efficient on the narrow strings compared to the wider strings, consistent with Eq. (2), and the effect of increasing the velocity from 50 to 100 m/s is also more pronounced, as expected.

Apart from demonstrating the effects of string geometry and aerosol velocity on material deposition, the sampling experiments serve to show that ENMs can be efficiently sampled onto micro- and nanostrings in just a few minutes, using a practically negligible amount of solution (in this case ~ 330 nL, corresponding to ~ 330 ng of sample, per experiment).

3.2. Dependence of string resonator sensitivity on geometry

Relative frequency shifts were measured for strings of varying widths and lengths, following an instant power shift of the laser-Doppler vibrometer readout laser from 2 to 200 μW .

Fig. 6a shows relative frequency shifts of SiN strings determined experimentally as a function of the inverse of the string width. Each measurement was repeated three times, and the average relative frequency shift and the standard deviation were calculated from these measurements. As expected from Eq. (4), the relative frequency shift increases linearly with the inverted string width. From the slope of the linear fit and Eq. (4), the absorbed power is extracted to be 1.8 nW, which is approximately 10 ppm of the readout laser power.

Fig. 6b shows experimentally determined relative frequency shifts of silicon-rich silicon nitride (SRN) strings as a function of string length. Again, each measurement was repeated three times, and based on these measurements the average relative frequency shift and standard deviation were calculated. In this case, the linear dependence of the relative frequency shift on string length, which is expected from Eq. (4), is not obvious, but the tendency of the relative frequency shift increasing with string length is clear. If the absorbed power is calculated from the slope of the linear fit, it becomes 2.3 μW , approximately 1% of the readout laser power.

The difference in absorbed power for the SiN strings and the SRN strings is not surprising and probably just an effect of the two different materials exhibiting different absorbances of the 633 nm laser light. A further comparison of the two sets of measurements suggests that SRN has a higher thermal conductivity than SiN, as the relative frequency shifts for short SRN strings trend towards values below the linear fit of the data set, indicating dissipation of heat.

Generally, the higher the heat flux into a string, the lower its resonance frequency. During a frequency measurement, the readout laser will provide a constant heat input to the resonator. However, heat will also be passed on from the resonator to the silicon frame of the chip. Thus, each measurement is characterized by a certain relaxation time, in which thermal equilibrium is established. Thermal relaxation effects are more pronounced for fibers that cannot conduct heat fast, e.g. strings that are long and/or narrow.

3.3. NAM-IR spectroscopy of polymeric micelles

Block copolymers are increasingly used for nanoscale engineering, as they can be custom synthesized to fulfill regioselective needs. Amphiphilic block copolymers are ideal for creating self-assembled structures with specialized properties. In this study,

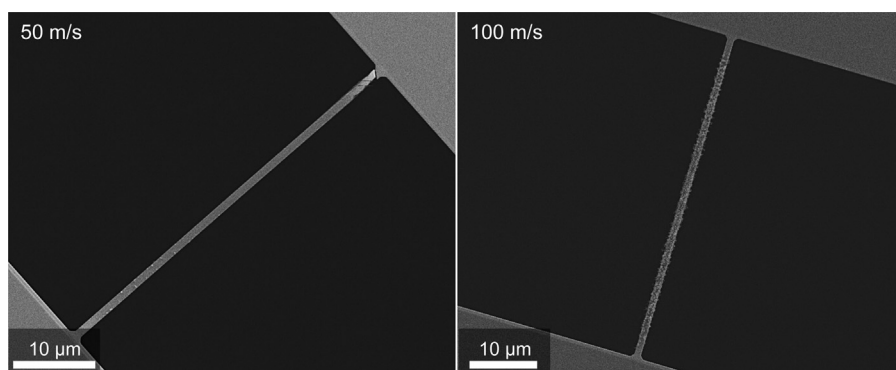


Fig. 5. SEM images of two narrow SiN strings (1000 nm wide and 50 μm long) coated with PEG-*b*-PAEMA-*b*-PCMA micelles at different aerosol velocities, through electrospraying of a 1 mg/ml micelle solution.

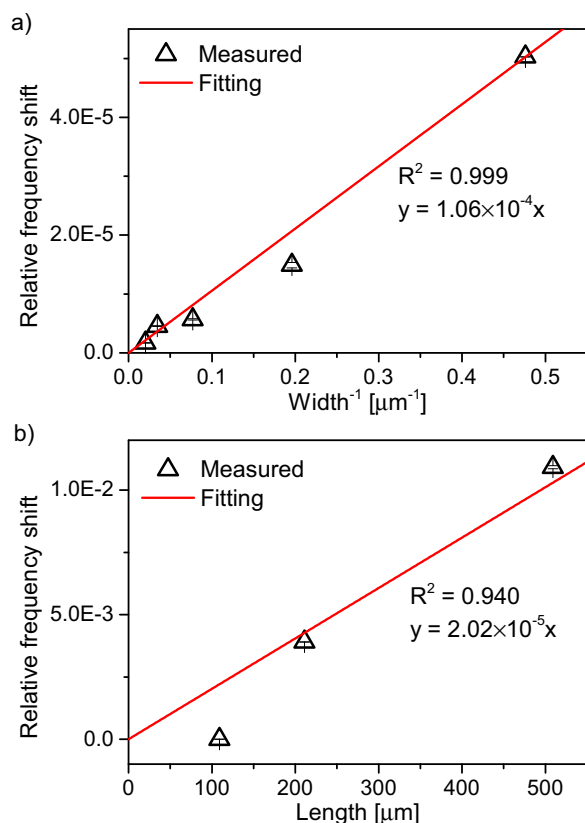


Fig. 6. (a) Relative frequency shifts of 214 μm long and 61 μm thick SiN strings of varying widths and (b) relative frequency shifts of 5.5 μm wide and 185 nm thick SRN strings of different lengths. For all measurements, the readout laser was positioned at the center of the string with the laser power changed instantly from 2 to 200 μW. The error bars represent standard deviations, and the red lines are linear fits of the data points. (For interpretation of the references to color in this legend, the reader is referred to the web version of the article.)

PEG-*b*-PAEMA-*b*-PCMA micelles were used as an example ENM. The micelles have previously been used for development of a pH nanosensor [15], and possess a hydrophobic and photocrosslinkable core, a shell region in which fluorophores can be bound, and a PEG corona.

SRN strings were coated with non-crosslinked PEG-*b*-PAEMA-*b*-PCMA micelles using either an electrospray or a standard jet nebulizer setup, and IR spectra covering the wavenumber range from 925 to 1920 cm⁻¹ were obtained using NAM-IR (Fig. 7a). The NAM-IR spectra were normalized with respect to the QCL power. Fig. 7b shows a NAM-IR spectrum compared to an ATR-FTIR reference spectrum. In the experiment, from which the spectrum in Fig. 7b stems, the micelles were sampled onto a 210 μm long, 3 μm wide SRN string using a jet nebulizer. The particles were sampled at a flow velocity of 108 m/s for 5 min. The concentration of the micelle solution used for generating the aerosol was 0.2 mg/ml. The obtained NAM-IR spectrum is in good agreement with the reference spectrum, suggesting that NAM-IR is suitable for chemical analysis of small amounts of dispersed and complex ENMs.

3.4. Identification of polystyrene in polluted samples

In order to investigate if NAM-IR could identify components of interest in polluted samples, a sequence of experiments was performed, in which solutions of polystyrene (PS) latex beads were spiked with increasingly concentrated solutions of polyvinylpyrrolidone (PVP). In this way, the PS samples were

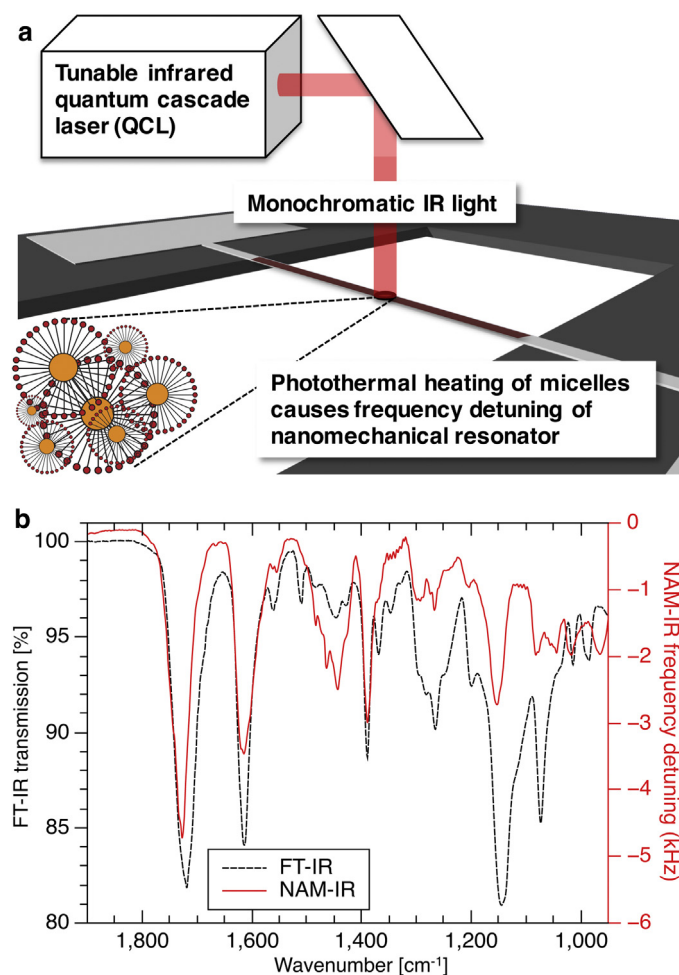


Fig. 7. (a) Schematic drawing of the NAM-IR method. The micelles collected on the nanomechanical string resonator are irradiated with monochromatic IR light from a QCL. The photothermal heating of the micelles causes the string to detune. An absorption spectrum is recorded by measuring the IR-wavelength-dependent frequency detuning of the nanomechanical resonator. (b) A NAM-IR spectrum with a resolution of 2 cm⁻¹ of PEG-*b*-PAEMA-*b*-PCMA micelles, compared to the corresponding ATR-FTIR spectrum.

polluted in a controlled manner, with a component known to have IR absorption peaks in the same region as PS.

Mixtures of PS and PVP were sampled onto SiN strings using a standard jet nebulizer setup, and NAM-IR spectra were obtained in the wavenumber range 1150–1850 cm⁻¹. Fig. 8 shows measured NAM-IR spectra of PS/PVP mixtures in different ratios, compared to computationally generated spectra obtained by linear superposition of individual ATR-FTIR spectra of PS and PVP, in the relevant ratios. The NAM-IR spectra are normalized with respect to the QCL power.

In all measured NAM-IR spectra of PS/PVP mixtures, spectral elements from both PS and PVP are visible, with those for PVP becoming dominant as higher concentrations of this polymer are added. For instance, the large peak at 1685 cm⁻¹, caused by carbon–oxygen double bonds and deriving from PVP, increases in intensity, while the sharp PS-derived peak at 1484 cm⁻¹, stemming from carbon–hydrogen bonds in the aromatic ring, is fading out.

Based on these initial measurements, the NAM-IR method appears to be well suited to analyze mixed and polluted samples. Peaks generally appear sharp and with little tendency to merge, making individual spectral features relatively clear. However, currently samples with absorption peaks of very different intensities are difficult to measure; for large intensities, the duty cycle of the IR

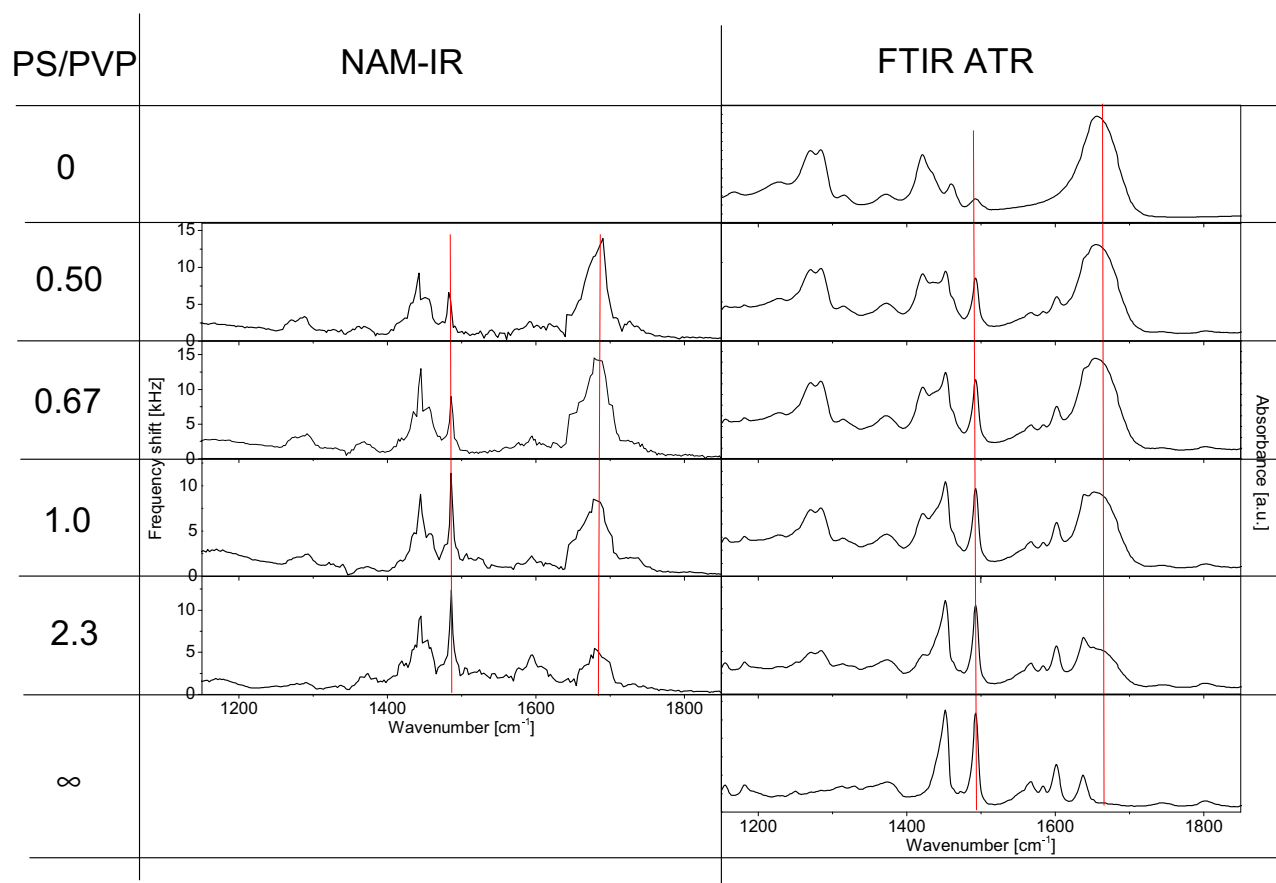


Fig. 8. Left column: NAM-IR spectra of different compositions of PS and PVP. Increasing concentrations of PVP is added to PS starting from the bottom of the column. Right column: measured ATR-FTIR spectra of pure PS (bottom) and PVP (top), along with computationally generated spectra obtained by linear superposition of the individual ATR-FTIR spectra of PS and PVP, in the relevant ratios. The vertical red lines indicate peaks stemming primarily from PS (at 1484 cm^{-1}) and PVP (at 1685 cm^{-1}), respectively. (For interpretation of the references to color in this legend, the reader is referred to the web version of the article.)

laser has to be quite low, in order for the phase-locked loop to stay locked in, and this makes the smaller absorption peaks difficult to identify.

4. Conclusion

Nanomechanical IR spectroscopy (NAM-IR), with its effective intrinsic ENM sampling, has been presented as an excellent tool for fast chemical analysis of minute sample amounts.

The geometry of the mechanical string resonators used for NAM-IR is important, and in accordance with the appertaining theory, the results presented here show that long and narrow strings are preferable for both efficient sampling and sensitive measurements. However, the longer relaxation time for long and narrow strings will have to be accounted for.

NAM-IR is still in its infancy, and accordingly several issues can be improved, including the bulky and not very user-friendly experimental setup, and the IR laser. Furthermore, the sensitivity when measuring a mixture, or another complex sample, can be enhanced by improving the frequency setup to measure larger intensity differences.

However, even at this early stage, NAM-IR exhibits several extraordinary features; the time necessary for preparing a sample for IR spectroscopy is no more than a few minutes with this method, a drastic improvement from the ~ 2 days that is typically needed for freeze-drying of a sample for ATR-FTIR, which is still considered state-of-the-art within IR spectroscopy. With respect to the necessary amount of sample, NAM-IR also outmatches

ATR-FTIR, requiring only picograms of deposited sample as opposed to milligrams. NAM-IR spectra closely resemble those of ATR-FTIR and can be obtained at similar resolutions.

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Biographies

Alina J. Andersen obtained her B.Sc. and M.Sc. in biophysics from the University of Copenhagen in 2006 and 2008, respectively. She received her Ph.D. in nanomedicine from the Department of Pharmacy at University of Copenhagen in 2013. Since then, she has worked as a postdoc at the Technical University of Denmark under Silvan Schmid and Anja Boisen. Her current research interests include micro- and nanomechanical resonators for sensing and analysis, as well as micro- and nanofabricated devices for oral drug delivery.

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E.K. Pramodkumar received his M.Sc. degree in applied chemistry from Mahatma Gandhi University Kerala, India, in 2003 and M.Phil. degree in organic chemistry from Cochin University of Science and Technology, India, in 2005. He joined as a junior research fellow at Indian Institute of Technology Guwahati in 2005. In 2009 he moved to Technical University of Denmark and started his Ph.D. studies under the supervision of Professors Thomas L. Andresen and Kristoffer Almdal. He obtained his Ph.D. degree in 2012 on polymeric nanoparticle synthesis. He is currently working as a postdoc at DTU Nanotech under Professor Thomas L. Andresen. His current research interests include development of nanoparticles for sensing, imaging and drug delivery applications.

Thomas L. Andresen received his Ph.D. in chemistry at the Technical University of Denmark (DTU) in 2005. He continued his career as R&D Director in the biotech industry before being employed at Risø, National Laboratory as a senior scientist. In 2012 he was appointed full professor at DTU Nanotech, where he is heading the Center for Nanomedicine and Theranostics. Professor Andresen's research interests lie at the interface between organic synthesis, biophysical chemistry, and cell biology. He focuses on the design of nanosystems for drug delivery, diagnostic, and sensor applications, where quantification of molecular interactions and transport of synthetic materials at biological interfaces is a main area of interest.

Anja Boisen is professor at DTU Nanotech and has many years experience in nanomechanical sensors. She is heading a DNRF and Villum Center of excellence focusing on nanomechanical sensors and new microfabricated solutions for oral drug delivery.

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